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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/596,086

05/30/2006

Dominique Jean-Pierre Mabire

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1676

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EXAMINER

TUCKER, ZACHARY C

ART UNIT

PAPER NUMBER

1624

MAIL DATE

DELIVERY MODE

05/15/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/596,086	Applicant(s) MABIRE ET AL.	
	Examiner Zachary C. Tucker	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4,6,8 and 10-30 is/are pending in the application.
4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 4,16,24,25 and 28 is/are allowed.
- 6) ☒ Claim(s) 1-3,6,8,12-14,17,20,23,29 and 30 is/are rejected.
- 7) ☒ Claim(s) 10,11,15,18,19,21,22,26 and 27 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>2Nov06</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 17, 20 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 8, 17, 20 and 23 are not enabled because the compounds of the invention, which are inhibitors of the PARP-1 enzyme (as demonstrated in the specification, pages 35 and 36), could only worsen a disease that is the result of too little PARP-1 activity. The recitation of "a PARP-mediated disorder" as claims 8, 17, 20 and 23 specify, includes those caused by not enough PARP activity. Increased sensitivity to carcinogenesis is a documented result of PARP deficiency, as evidenced by Virág and Szabó, "The Therapeutic Potential of Poly(ADP-Ribose) Polymerase Inhibitors" *Pharmacological Reviews*, vol. 54(3), pages 375-429 (2002) – (see page 418, lines 12-15). This could only be made worse by administering to a subject an inhibitor of PARP-1. Since compounds of the invention are PARP-1 inhibitors, diseases mediated by other isoforms of PARP, such as PARP-2, are not treatable with a compound according to the present invention because said compounds do not affect PARP-2 enzyme.

The so-called "Wands factors," as prescribed by the court for determinations of whether or not claimed subject matter is enabled by a given disclosure (*In re Wands*, 858

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F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) have not been addressed in this rejection, because the claimed invention, which is a method of treatment of any and all diseases mediated by PARP is impossible with any amount of experimentation. Broadest reasonable interpretation of claims 8, 17, 20 and 23 includes those diseases associated with too little PARP activity, and those associated with isoforms of PARP other than the one which is inhibited by the compounds of the present invention, which diseases cannot be treated by said compounds.

Claims 8, 17, 20 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8, 17, 20 and 23 are indefinite in scope, for the reason that the full scope of all diseases mediated by PARP is not known to those of ordinary skill. Many diseases associated with PARP activity (or lack thereof) are known, but even the term “diseases in which PARP plays a role” would be indefinite because one of ordinary skills’ knowledge pertaining to the PARP enzyme’s role in disease is constantly changing. Scientific conclusions are subject to further inquiry as new data emerge. Thus, a method according to one of claims 8, 17, 20 and 23, if patented, would be subject to different interpretations at different times, sometimes narrowing, sometimes broadening. Claim 26 is also indefinite because the claim does not point out which isoform of PARP is the mediator of the disorders specified in the claims (*i.e.*, PARP-1 or PARP-2, *et cetera*).

The Virág and Szabó reference, cited hereinabove in the rejection of claims 8, 17, 20 and 23 under the first paragraph of this statute, describes PARP-1 and PARP-2 at pages 378 and 379.

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From another point of view, PARP enzymes are not the mediator of any disease process. These enzymes respond to disease processes, sometimes making them worse, and sometimes promoting recovery from cellular injury. The word “mediated” implies a causative factor. PARPs do not cause any disorders. The diagram on page 384 (fig. 4) titled "The Yin-Yang of PARP activation" of the reference authored by Virág and Szabó cited above, depicts how this is true. Thus, claims 8, 17, 20 and 23 refer to disorders which do not exist. PARPs are a normal constitutive element of cellular biology. Their presence does not cause disorders.

Lastly, claims 8, 17, 20 and 23 are further indefinite because, as evidenced by Virág and Szabó, page 379 (last paragraph in column two) and pages 382-385, the role of PARPs in disease processes remains to be fully elucidated. So it logically follows that one of ordinary skill having knowledge of the state of the art with respect to the therapeutic application of PARP inhibitors at the time the invention was made, did not understand the full scope of the term “PARP mediated disorder,” even if the isoform was limited to only PARP-1.

Claim 13 is rejected under the second paragraph of 35 U.S.C. 112, for being indefinite because it fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites three different steps in the process specified therein: “a),” “b),” and “c).” All three are specified, without any suggestion by the claim's language that these are alternatives, not to be conducted sequentially, instead of (as the claim language suggests) all in the same embodiment of the process, which presents logical problems in the claim's interpretation. The word “or” should therefore be inserted between the end of embodiment

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“b)” and embodiment “c).” Claim 13 has been examined on the merits in this Office action as though “or” appeared between the end of embodiment “b)” and embodiment “c).”

Claim 30 is rejected under the second paragraph of 35 U.S.C. 112, for being indefinite because it fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is indefinite, in addition to being indefinite for depending from an indefinite base claim (claim 13), because it recites the limitation "A pharmaceutical composition made by the process of claim 13." There is insufficient antecedent basis for this limitation in the claim, as claim 13 is drawn to a process for preparing a compound as claimed in claim 1, not a process for making a pharmaceutical composition.

Cancellation of claims 8, 17, 20, 23 and 30 is recommended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

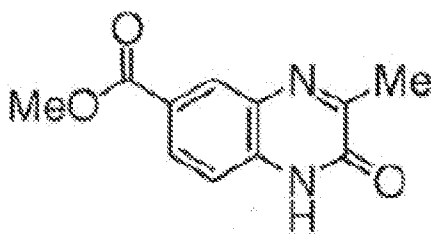
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 6, 13, 14 and 29 rejected under 35 U.S.C. 102(b) as being anticipated by Katoh et al, "Synthesis of Quinoxaline Derivatives Bearing the Styryl and Phenylethynyl Groups and Application to a Fluorescence Derivatization Reagent" *Heterocycles*, vol. 52(2), pages 911-920 (2000).

Katoh et al discloses a process for making quinoxaline derivatives, in which 6-methoxycarbonyl-3-methyl-styrylquinoxaline-2(1*H*)-one, which was an attempted fluorescence derivitization reagent for detection of amines, was produced by a synthesis comprising reaction of 6-methoxycarbonyl-3-methyl-2-oxo-quinoxaline and

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phenylacetylene. The synthesis scheme for production of 7-methoxycarbonyl-3-methyl-2-oxo-quinoxaline is shown on page 913, as "Scheme 1." The reaction of ethyl pyruvate and methyl 3,4-diamino benzoate produces a mixture of structural isomers, one of which is the 6-methoxycarbonyl-3-methyl-2-oxo-quinoxaline isomer, whose structure is represented by the diagram shown here:



, is designated compound "1a," and is a compound according to claims 1, 2 and 29, wherein X is N; R¹ is C₁-C₆ alkyl (methyl); n=0; R² and R⁴ are joined to form =O; and R³ is (a-3), wherein R⁸ is C₁-C₆ alkyl (methyl).

Claims 6 and 14 are anticipated by Katoh et al by virtue of the fact that compound 1a, whose structure is shown above, was crystallized from EtOH (page 916). The composition formed by solution of compound 1a in EtOH is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to claims 1 or 2, respectively (claims 6 and 14 depend from claims 1 and 2, respectively). EtOH is a pharmaceutically acceptable carrier for rubbing compounds, lotions, tonics and colognes, as discussed in The Merck Index, 13th Ed., page 670, in the monograph for "Ethyl Alcohol" ©2001 by Merck and Co., Inc.

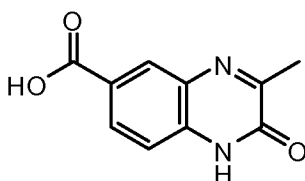
Claim 13 is anticipated by virtue of the fact that compound 1a, whose structure is diagrammed above, was made by a process according to embodiment "c)" of that claim. Ethyl pyruvate, which is a compound according to formula (XII) of that claim wherein Rⁿ is

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C₁-C₆ alkyl (ethyl), is reacted with methyl 3,4-diaminobenzoate, a compound of formula (XI) of claim 13, in ethanol for 20h at room temperature (described on page 916).

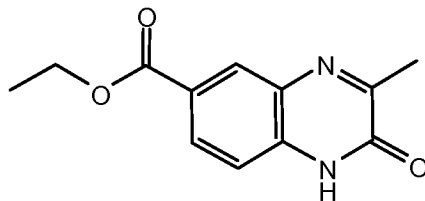
Claims 1-3, 13 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Blackburn et al, "The Preparation of 3-Methyl-6- and -7-carboxy-2-quinoxalones" Journal of Organic Chemistry, vol. 26, pages 2818.

Blackburn et al discloses a process for synthesis of 3-methyl-6- and -7-carboxy-2-quinoxalones (2-oxo-quinoxalines). On page 2808, near the top of column 1, the synthesis of "3-methyl-6-carboxyquinoxalone-2 hydrate" is described. 3-methyl-6-carboxy-quinoxalone-2 has a structure represented by the following diagram:



and is a compound according to claims 1-3 and 29, wherein X is N; R¹ is C₁-C₆ alkyl (methyl); n=0; R² and R⁴ are joined to form =O; and R³ is (a-2).

On page 2809, in column 1, just below where the synthesis of 3-methyl-6-carboxy-quinoxalone-2 is described, the synthesis of 3-methyl-6-carbethoxyquinoxalone-2 is described, wherein 3-methyl-6-carboxyquinoxalone-2 is directly esterified with ethanol. 3-methyl-6-carbethoxyquinoxalone-2 has a structure represented by the following diagram:



and is a compound according to claims 1, 2 and 29, wherein X is N; R¹ is C₁-C₆ alkyl (methyl); n=0; R² and R⁴ are joined to form =O; and R³ is (a-3), R⁸ is C₁-C₆ alkyl (methyl).

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Product by process claims, like instant claim 29, are not limited to the manipulations of the recited steps, only to the structure implied by the steps, so the compounds reported by Blackburn et al, though produced by a different synthetic scheme from the one specified in instant claim 13, anticipate instant claim 29.

On page 2809, in the paragraph spanning columns one and two, Blackburn et al reports synthesis of the above-diagrammed carbethoxyquinoxalone-2 derivative by a procedure described by Zehra, *Ber.*, vol. 23, pages 3629 (1890). In this synthesis, ethyl 3,4-diaminobenzoate was reacted with ethyl pyruvate to provide a mixture of the 6-carbethoxy and 7-carbethoxy derivatives. The process of instant claim 13 is anticipated by this disclosure in Blackburn et al, insofar as the production of 3-methyl-6-carbethoxyquinoxalone-2 derivative is concerned, in the manner set out in the rejection of claims 1, 2, 6, 13, 14 and 29 under 35 U.S.C. 102(b) as being anticipated by Katoh et al.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipate by U.S. Patent 7,115,630 (Mabire et al), in view of the publication date of the WO publication upon which said patent is based, which is WO 02/28837, published 11 April 2002.

The Mabire et al patent discloses two compounds according to claims 1 and 2 in column 113, compounds #153 and 190, which anticipate claims 1 and 2 wherein X is CR⁵, wherein R⁵ is hydrogen; R¹ is C₁-C₆ alkyl (methyl); n=0; R² and R³ together form =O; and R⁴ is arylC₁-C₆ alkyl (benzyl, compound #153 and phenethyl, compound #190, respectively).

Claim Rejections - 35 USC § 103

Claims 8 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,028,606 (Venet et al).

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At the time the invention was made, the method according to claim 8 and the combination according to claim 12 would have been obvious to one of ordinary skill in the art, given the teachings of Venet et al.

The difference between Venet et al and the method according to instant claim 8 and the combination according to instant claim 12 is that Venet et al does not specifically disclose such a method or combination, but expressly suggests both.

Venet et al discloses (1H-azol-1-yl-methyl)substituted quinoxaline derivatives, which are pharmaceuticals for the decreasing of plasma elimination of retinoic acids, and which inhibit the formation of androgens from progestins, and/or inhibit the action of the enzyme complex aromatase which catalyzes the formation of estrogens from androgenic steroids in mammals.

In Table 9, in columns 43 and 44, for example, compound #58, prepared by the procedure outlined in Example 20 in that patent (which appears in columns 34-35), is a compound according to formula (I) as specified in instant claim 8 and formula (I) as specified in instant claim 12, wherein X is N; R¹ is C₁-C₆ alkyl (methyl); n=0; R² and R⁴ are both hydrogen; R³ is (c-2), with R¹⁰ being -H.

In Table 9, compound #120, prepared by the procedure outlined in Example 20, is a compound according to formula (I) as specified in instant claim 8 and formula (I) as specified in instant claim 12, wherein X is N; R¹ is C₁-C₆ alkyl (methyl); n=0; R² is hydrogen; R⁴ is C₁₋₆ alkyl (isopropyl); R³ is (c-4), with R¹⁰ being -H.

Venet et al teaches that the compounds disclosed in that patent have utility in the treatment of carcinoma (col. 19, lines 45-49). As applicants can appreciate, carcinoma is, in the broadest reasonable interpretation, a "PARP mediated disorder," as evidenced by the Virág and Szabó reference, cited hereinabove in the rejection of claims 8, 17, 20 and

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23 under the first paragraph of 35 U.S.C. 112, for lack of enablement. Pages 412-414 of Virág and Szabó describe the use of PARP inhibitors for the treatment of various forms of cancer. Thus, it would have been obvious at the time the invention was made to treat a PARP mediated disorder with a compound disclosed by Venet et al. The motivation to do so would have been to improve the health of the subject being treated.

Venet et al also teaches that combinations of the compounds with retinoic acid are advantageous (col. 23, lines 10-20). Retinoic acid is, in the broadest reasonable interpretation, "a chemotherapeutic agent," thus, a combination according to instant claim 12 is expressly suggested by Venet et al. Thus, at the time the invention was made, it would have been obvious to incorporate a compound disclosed by Venet et al with a chemotherapeutic agent, wherein the chemotherapeutic agent is a retinoic acid. The motivation to do so would have been to provide a therapeutic combination for the treatment of acne, or for retarding the effects of aging of the skin and generally to improve the quality of the skin (col. 23, lines 15-20 of Venet et al).

Claims 6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mabire et al, applied against claims 6 and 8 as set forth hereinabove in the rejection of claims 1 and 2 under 35 U.S.C. 102(b).

The difference between the disclosure of Mabire et al and the method of instant claim 8 is that Mabire et al does not specifically disclose a method of treating a "PARP mediated disorder" in a subject, comprising administering a compound according to formula (I) as specified in instant claim 8, rather it is expressly suggested in the Mabire et al patent to do so.

Mabire et al, in col. 26, lines 35-57, expressly suggests treatment of "anoxic and ischemic injuries (ischemic stroke, cardiac arrest)" with a compound of the invention

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disclosed in that patent. As applicants can appreciate, ischemic stroke and cardiac arrest (a.k.a. myocardial infarction) is a "PARP mediated disorder" in the broadest reasonable interpretation, as evidenced by the Virág and Szabó reference, cited hereinabove in the rejection of claims 8, 17, 20 and 23 under the first paragraph of 35 U.S.C. 112, for lack of enablement. Pages 396-399 of Virág and Szabó teach that stroke and myocardial infarction (page 399) are "PARP mediated disorder[s]," in the broadest reasonable interpretation of the term.

The motivation to administer a compound according to the invention disclosed in Mabire et al to a subject would be to treat ischemic stroke or myocardial infarction (cardiac arrest).

The difference between the disclosure of Mabire et al and the pharmaceutical composition according to instant claim 6 is that Mabire et al does not specifically disclose a composition comprising a compound of instant claim 1 and a pharmaceutically acceptable carrier, rather such a composition is expressly suggested in Mabire et al.

Col. 27, line 11 to col. 28, line 10 of Mabire et al sets out the teachings that compounds of the invention disclosed therein are advantageously "formulated into various pharmaceutical forms for administration purposes."

The motivation to formulate compounds of the invention disclosed by Mabire et al into a pharmaceutical composition comprising a compound according to formula (I) as specified in instant claim 1 and a pharmaceutically acceptable carrier would have been to provide ease of therapeutic use of the compounds.

Allowable Subject Matter/Cited of Interest

Claims 4, 16, 24, 25 and 28 are allowed.

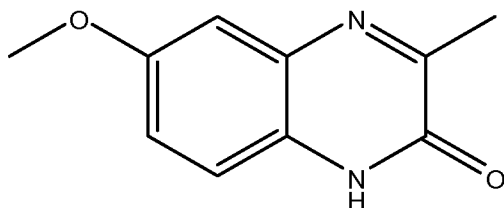
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No compound according to instant claim 4 was found in a search of the prior art. Since claims 16, 24, 25 and 28 depend from allowable claim 4, they are allowed as well. The closest prior art with respect to compounds according to instant claim 4 is the Blackburn et al, Katoh et al and Venet et al references cited in this Office action.

Cited of interest, as close prior art with respect to the compounds of the present invention as well, is:

Yolles and Schultz, "Quinoxaline Studies. I. The Preparation of 2-Hydroxy-3-methyl-6-methoxyquinoxaline and 2-Hydroxy-3-methyl-7-methoxyquinoxaline" Journal of the American Chemical Society, vol. 71, pages 2375-2377 (1949).

which reports synthesis of 2-hydroxy-3-methyl-6-methoxyquinoxaline, whose structure is represented by the diagram shown here (as the tautomeric form):



The compound is excluded from the scope of instant claim 1, however because an alkoxy group R³ may not be bonded directly to the quinoxaline ring system core - an intervening carbon atom must at least be present, to which R³ is optionally bonded.

Claims 10, 11, 15, 18, 19, 21, 22, 26 and 27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 9:00am to 5:00pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

**/Zachary C. Tucker/
Primary Examiner
Art Unit 1624**